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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/692,938	10/20/2000	James L. Meyerhoff	Army 126	6469

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EXAMINER	
GUPTA, ANISH	
ART UNIT	PAPER NUMBER
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/692,938	Applicant(s) MEYERHOFF ET AL.	
	Examiner Anish Gupta	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, 3, 5, 7, 10, the "Pro-NH^{2}" is supposed to be "Pro-NH_2".

Claim 4 and 6 are redundant because claim 1 already implies the presence of a pharmaceutically acceptable carrier by its definition.

Claim 7 recites "and/or". This is improper since it is unclear when the disease is to be "treated" and when it is supposed to be "prevented". The claim does not distinguish any different method steps from treating and preventing.

In claim 7 and 10, applicants are requested to place the limitation "under time and conditions to treat said disease" after the word "ingredient." As currently claimed, it is unclear as to the duration of the therapy.

In claim 10, it is unclear what it the intended meaning of "other nitrone." Applicants are requested to clarify.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 7-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment ischemia, does not reasonably provide enablement for the treatment or prevention of other neurological and neurobehavioral disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to enable the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to a method of treating neurological disorders using tripeptide that mimic TRH activity.

(2) The state of the prior art

The art provides guidance for TRH peptides effecting in the treatment of depression and schizophrenia, see The state of the art for Alzheimer's disease can be summed up by the Patel reference, which teach that Alzheimer's disease is known to be difficult to treat and that there is neither a clear understanding of the origin and pathophysiology of the disease no an animal model of illness (see page 81). Furthermore, it is well established in the art that acetylcholine transmitting neurons and their target nerve cells are particularly affected. Even a therapeutic strategy involving replacement or enhancement of acetylcholine within the brain would probably not halt the progression of Alzheimer's disease. In conclusion, Patel states that the search for an effective cognition-enhancing therapy has so far proved elusive.

Moreover the art has also recognized the ineffectiveness of therapeutics on the regeneration of motor neurons after a CNS injury. For example, Merck Manual states that severed or denervated nerve process in the cord cannot recover and any dysfunction beyond six months likely to be permanent (see page 1464). The Merck Manual also states, for lower and upper motor neuron diseases, "[t]here is no specific treatment. Physiotherapy may help to maintain muscle function."(see page 1513). Clearly therefore, the art recognizes a difficulty in the treatment of CNS disorders .

National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health, on their web site, discloses that there are no cures for either ALS or Parkinson. Further, although their are treatments available, the web site stats, for Parkinson's,

"there is no way to predict or prevent the disease." (See page 11 of the Parkinson's web print out). NINDS also discloses similar problems associated with the prevention of ALS.

Finally, the art recognizes the effectiveness of Nitrones in treating Focal Ischemia, however, the art does not establish that these compounds would be effective in treat, let alone preventing, diseases such as ALS, Parkinson's, Alzheimer's and the like.

(3) The relative skill of those in the art

The relative skill of the those in the art is high.

(4) The predictability or unpredictability of the art

Considering that Alzheimer's disease known to be difficult to treat and that there is neither a clear understanding of the origin and pathophysiology of the disease no an animal model of illness and that the search for an effective cognition-enhancing therapy for AD has so far proved elusive, the unpredictiablity of treatment and prevention of Alzheimer's is very high. Similarly, for the treatment of neurological disorders, where there involves the regeneration of motor neurons, the art is similarly unpredictable since the art does not specify any specific treatment.

(5) The breadth of the claims

The claims are to a method of treating and preventing neurological diseases by the administration of the peptide pGlu-Glu-Pro alone or in combination of a nitrones. The neurological disorders claimed include, Alzheimer's spinal injuries, brain stem injuries, loss of

motor function and loss of cognitive function. The claims do not recited how such disorders are to be treated, just that these disorders are to be treated. Further, the claims also state that such disorders can be prevented. Therefore, in the broadest scope of the clams, the claims read on a method wherein diseases such as ALS, Parkinson's and Alzheimer's are prevented.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples

The specification provides guidance on the treatment of depression using TRH like peptides such as pGlu-Glu-Pro. The specification goes into great detail, using animal models, for the effectiveness of the peptides in anti-depressive effects. However, the specification does not provide ample guidance to allow for the treatment of all neurological disorders and CNS injuries as claimed. Infact, the specification is void of any guidance as to the how the neurological disorders are to be treated and what endpoints are to be achieved. Working examples for these disorders are necessary since there exists an intrinsic inability of CNS neurons to mount a regenerative response. For Alzheimer's disease, the art has indicated that to date, there is neither a clear understanding of the origin and pathophysiology of Alzheimer's Disease nor an animal model of the illness. This is also evidence of the extreme difficulty and unpredictably in treatment of Alzheimer's Disease. Further, disease such as Alzheimer's there is no known method nor pharmaceutical that can prevent the onset of this disease. In the instant specification, there is very little guidance provided in the way of working examples that the claimed compounds would be effective in the treatment of Alzheimer's, ALS or Parkinson's or other similar disorders. The art

has yet to recognize effective cognition-enhancing therapy for AD, as summarized by Patel. Furthermore, the specification does not provide any guidance with respect to prevention of the neurological disorders. As stated above and as established by the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health, there is no cure for ALS or Parkinson's, nor is there a proven therapy that will prevent or reverse the course of the disorder (see Web page print out). The reference also states that the drug approved by the FDA drug also extends the time before a patient needs ventilation support. Riluzole does not reverse the damage already done to motor neurons (See page 4 of the Web Print out).

Applicants specification is similar to the disclosure discussed in *Ex parte Sudilovsky*, [sic] 21 U.S.P.Q2d 1702 (BPAI 1991) where it was held that the disclosure was non-enabling since:

"[t]he specification, though highly detailed, is devoted solely to a description of compounds stated to be known ACE inhibitors. The remainder of the specification is directed to how to make tablets and solutions for injection. Any disclosure regarding utility is confined to broad allegations and suggestions without substantiating working example. As stated in In re Glass, 492 F.2d 1228, 181 USPQ 31, 35 (CCPA 1974), 'the strong feeling one gets from reading the entire specification is that either appellant did not have possession of the details of a single operative process or, if he did, he chose not to divulge them.'"

Similarly, Applicants specification discloses compounds known to mimic THR activity and the specification teach how to make pharmaceutical formulations. However, the disclosure, with regard to method of treating neurological disorders, is confined to broad allegations and suggestions without substantiating working examples. Although working examples are not necessary in the specification, lack of a working example, however, is a factor to be considered,

especially in a case involving an unpredictable and undeveloped art where in the case of neurological disorders, treatment is basically ineffective. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to substantiate them. *In re Novak*, 306 F.2d 924, 134 USPA 335 (CCPA 1962) 4; *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971).

(8) The quantity of experimentation necessary

Since the disclosure has not provided evidence of record of analogous activity for similar compounds and the art has recognized that treatment of neurological disorders, such as AD, ALS or Parkinson's, undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-2 are are rejected under 35 U.S.C. 102(b) as being anticipated by Cremades et al.

The claims are drawn to a pharmaceutical formulation comprising p-Glu-glu-Pro-NH2.

The reference of Cremades et al. teach that the peptide pGlu-Glu-Pro -amide was effective in increasing levels of triiodothyronine and tetraiodothyronine when administered subcutaneously to mice (see abstract and page 64). The reference states that pGlu-Glu-Pro was administered at a concentration of 100μg in 300μl of aqueous solution (see page 64, column 2). Thus the reference teach a pharmaceutical formulation of the peptide, as indicative of the subcutaneous administration, with the aqueous solution as the carrier. Thus the reference anticipates the claimed invention.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can normally be reached on (703)308-2923. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Anish Gupta

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